

--19. (amended) A kit or case comprising:

a) an oligomeric conjugate according to claim 1, substituted by protonable residues, said residues being protonated in a weak acid medium, said protonation leading to destabilization of cellular membranes said oligomeric conjugate being able to comprise a recognition signal, which is previously fixed or not on said conjugate, wherein said recognition signal is a ligand for a cell membrane receptor

b) at least one biological molecule to transfer,

c) optionally reagents enabling the possible binding of the recognition signal on the above-said oligomeric conjugate, and

d) reagents enabling the transfer of the biological molecule in the cytosol and/or the cell nucleus.-

R E M A R K S

This application has been amended in a manner that places it is believed to place it in condition for allowance at the time of the next Official Action.

At the outset, applicants note with appreciation the rejoinder of claims 1-8 and 11-14. As noted on page 2 of the outstanding Official Action, claims 1-14, 17, and 19 are under consideration in the present application.

Claims 5-14, 17, and 19 were objected to under 37 CFR §1.75(c) as allegedly being in improper form. It is believed

that the present amendment obviates this objection. Claims 5-14, 17, and 19 have been amended to recite proper claim pendency.

In the outstanding Official Action, claims 1-4 were objected to for allegedly containing several informalities. In view of the present amendment, these objections are traversed.

It is believed that the amendment to claims 1-4 obviates these informalities. The pending claims have been amended so that all sentences begin with an article. Claims 1-4 have been amended so that arrows and dashes are no longer recited in the claims. The claims have been amended in order to incorporate the active voice. Moreover, the English spellings of "quinolines", "pterines", and "pyridines" have also been utilized in the present specification. Applicants would like to thank the Examiner for his suggestions for overcoming these objections.

Claim 2 has been amended so that the phrase "present the additional properties" has been replaced with "have a PKA in aqueous medium lower than 8.0".

In the outstanding Official Action, claims 1-4 were rejected under 35 USC §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is believed the present amendment obviates this rejection.

Claims 1-4 were rejected for allegedly containing a broad range or limitation together with a narrow range or limitation falling within the same claim. However, claims 1-4

have been amended so that terms such as "advantageously", "particularly", and "preferably" are no longer recited in the claims.

The outstanding Official Action also alleged that it was unclear whether the claims require the substitution of free- NH_3^+ residues with protonable residues wherein the substitution occurs in a weak acid medium, or whether the claim requires substitution of NH_3^+ residues with residues that are protonable in a weak acid medium. It is believed that the claims have amended to more particularly point and distinctly claim the present invention.

Moreover, upon reviewing the specification, applicants respectfully submit that it is clear the residues accounting for the destabilization of cellular membranes through the property of being protonable in a weak acid medium. In fact, the Examiner's attention is respectfully directed to page 5, line 28, to page 6, line 2, wherein it is stated that the residues exhibit the property of being protonable in a weak acid medium. Thus, it is believed that this matter would be clear to one of ordinary skill in the art.

In the outstanding Official Action, it was alleged that the phrase "leading in such a weak acid medium to a destabilization of cellular membranes" was confusing. This phrase has also been amended to provide further clarity to the claims.

The outstanding Official Action also rejected the claims for relying on the term "correspond". Applicants traverse this rejection. It is believed that this term is described on page 6, lines 15-23. The specification provides that the expression "into which the protonatable residues do not correspond to the recognition signal recognized by a cellular membrane receptor" indicates that these residues are not used as ligands.

Moreover, the specification provides that a "molecular complex" is active as a recognition signal when it can be selectively recognized by a receptor. In other words, it plays the role of a ligand. It may be an agonist, or antagonist. In view of the present specification, it is believed that this term is definite to one of ordinary skill in the art.

In the outstanding Official Action, the use of the word "either" is also found to be confusing. The claims have been amended so that this term is no longer recited in the claims.

The outstanding Official Action alleged that claims 3 and 4 were indefinite because it was unclear in what manner the claims require protonable residues. However, claims 3 and 4 have been amended to clarify the compounds which comprise these protonable residues. Thus, it is believed that claims 3 and 4 are definite to one of ordinary skill in the art.

It is believed that claims 1-4 are definite to one of ordinary skill in the art.

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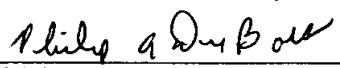
In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 1-14, 17, and 19, as presented. Allowance and passage to issue on that basis are accordingly respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Amend the claims as follows:

--1. (twice amended) An [Oligomeric] oligomeric conjugate positively charged, comprising:

[containing] an oligomer with a polymerization degree (PD) from 5 to 36 [30], formed from monomeric components having free NH_3^+ in a number equal to or higher than 50 % of the polymerization degree, wherein

[said oligomer being as follows:]

[-] a) the free NH_3^+ of [the above-mentioned] said monomeric components are substituted in a ratio of at least 50 %, [advantageously from 60 % to 95 %, particularly 80 to 90 % (this] said ratio being determined by nuclear magnetic resonance[)],] by protonable residues, said residues being protonated in a weak acid medium, said protonation leading to a destabilization of a cellular membrane [in a weak acid medium, leading in such a weak acid medium to a destabilization of cellular membranes],

[-] b) [the above-mentioned] said protonable residues [posses] possess [in addition] the following properties:

[→ they] said protonable residues contain a functional group enabling them to be linked to [the above-mentioned] said oligomer,

[→ they] said protonable residues [do not correspond to] are not recognized as a recognition signal [recognized] by a cellular membrane receptor,

[→ they] said protonable residues [can] comprise at least one free NH_3^+ group,

[-] c) the free NH_3^+ of [the above-mentioned] said monomers can be also substituted by [an] uncharged residues leading to a reduction of the number of positive charges in comparison to the same [oligomeric] oligomer before substitution,

[-] d) molecules constituting a recognition signal recognized by a membrane cellular receptor may be present:

[→ either] by substitution of some of the free NH_3^+ of [the above-mentioned] said monomers,

[→ either] on some of the uncharged residues leading to a reduction of the number of charges,

[→ either] on some of [the above-mentioned] said protonable residues leading to a destabilization of [the] a cellular [membranes] membrane, or

[→ or] by substitution of the free NH_3^+ (if it is present) of [the above-mentioned] said protonable residues leading to a destabilization of [the] a cellular membrane,

provided that:

1) the total number of the non substituted NH_3^+ functions is of at least 50 % of the polymerization degree,

2) the number of monomers initially carrying free NH_3^+ is substituted in a ratio of at least 50 % of the polymerization

degree by residues leading to a destabilization of the cellular membrane.--

--2. (amended) [Oligomeric] The oligomeric conjugate according to claim 1, wherein the protonable residues leading to a destabilization of cellular membranes[, present the additional properties:] wherein said protonable residues have a [- they are weak bases the] pK [of which] in aqueous medium [is] lower than 8. [so that a proportion higher than 50% of these bases linked to a cationic oligomer is not protonated in a neutral medium of pH 7.4].-

--3. (amended) [Oligomeric] The oligomeric conjugate complex according to claim 1, wherein [the] said protonable residues [leading to a destabilization of cellular membranes, present the additional properties] are compounds selected from the group consisting of:

[-] [they belong to the group of compounds comprising an imidazole ring] imidazoles,

[-] [they belong to the group of quinolins] quinolines,

[-] [they belong to the group of pterins] pterines, and

[-] [they belong to the group of pyridins] pyridines.-

--4. (amended) [Oligomeric] The oligomeric conjugate according to [anyone of claims] claim 1 [to 3], wherein [the]

said protonable residues [leading to a destabilization of the cellular membranes are:] comprise

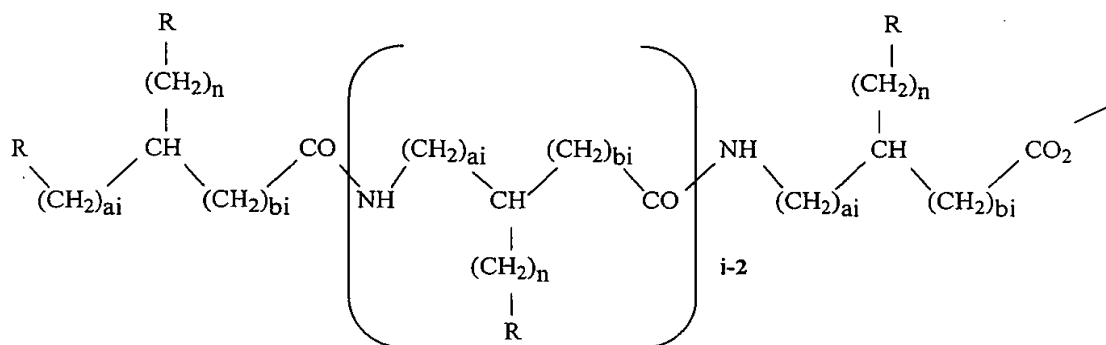
[-] alkylimidazoles in which the alkyl radical [comprises] has from 1 to 10 [, particularly from 2 to 6] carbon atoms, and [in which] only one [of the] nitrogen atom[s] of the imidazole ring is substituted.--

--5. (amended) [Oligomeric] The oligomeric conjugate according to [anyone of claims] claim 1 [to 4], wherein the protonable residues leading to a destabilization of cellular membranes are [chosen from:] selected from the group consisting of

histidine, 4-carboxymethyl-imidazole,
3-(1-methyl-imidazol-4yl)-alanine, 3-(3-methyl-imidazol-4yl)-alanine,
2-carboxy-imidazole, histamine, 3-(imidazol-4yl)-L-lactic acid,
2-(1-methyl-imidazol-4yl)ethylamine, 2-(3-methyl-imidazol-4yl)ethylamine,
 β -alanyl-histidine-(carnosine), 7-chloro-4(amino-1-methylbutylamino)-quinoline,
N4-(7-chloro-4-quinolinyl)-1,4-pentanediamine,
8-(4-amino-1-methylbutylamino)-6-methoxy-quinoline (primaquine),
N4-(6-methoxy-8-quinolinyl)1,4-pentanediamine, quininic acid,
quinoline carboxylic acid, pteric acid, nicotinic acid, and quinolinic acid.--

--6. (amended) [Oligomeric] The oligomeric conjugate according to [anyone of claims] claim 1 [to 5],

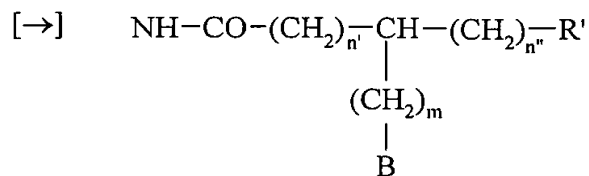
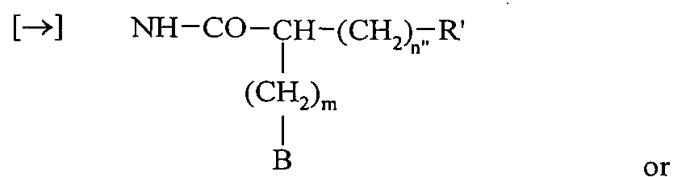
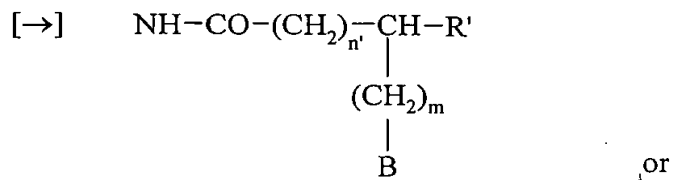
wherein the oligomeric conjugate contains an oligomer of the following formula:



wherein

- * ai is an integer varying from 0 to 10,
- * bi is an integer varying from 0 to 10,
- * i = degree of polymerization from 5 to 36 [50, and particularly 10 to 40, and preferably 20],
- * n = is an integer varying from 1 to 6, [and preferably 4,]

* R represents in a ratio of 50 % to 100 % (corresponding to a number u)



m is an integer varying from 1 to 6,

n' is an integer varying from 0 to 6,

n" is an integer varying from 0 to 6,

B is a weak base [as defined according to anyone of claims 2 to 4],

R' represents NH_3^+ (corresponding to a number p),
or NH (corresponding to a number q) substituted
by

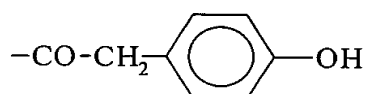
-CO-CH₃

-CO-(CHOH)_rH

r being an integer from 1 to
15, and preferably 1 to 7

-CO-(CH₂)_s-(CHOH)_rH

r being an integer from 1 to
15, [and preferably 1 to 7,]
and s being an integer from 1
to 6, [and preferably 6]



-SO₂-Flu

-CO-Flu

-CS-NH-Flu

Flu being a fluorescent molecule

* R represents in a ratio of 0 % to 50 %
(corresponding to f: $0 < f \leq u$)

[-] NH_3^+ (corresponding to a number j),

[-] NH (corresponding to a number k),

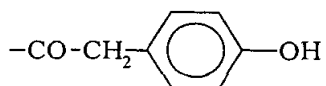
substituted by

-CO-CH₃

-CO-(CHOH)_rH

r being an integer from
1 to 15, [and preferably
1 to 7]

$-\text{CO}-(\text{CH}_2)_s-(\text{CHOH})_r\text{H}$ r being an integer from 1 to 15, [and preferably 1 to 7], and s being an integer from 1 to 6, [and preferably 6]



$-\text{SO}_2\text{-Flu}$

$-\text{CO-Flu}$

$-\text{CS-NH-Flu}$

Flu being a fluorescent molecule

$[-]\text{H}$ (corresponding to a number h)

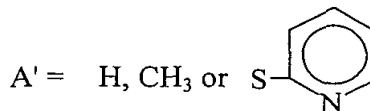
$[-]\text{CH}_2)_n\text{H}$, n being an integer from 1 to 6

(corresponding to a number h)

$[-](\text{CH}_2)_n\text{-OH}$ n being an integer from 1 to 6

(corresponding to a number h)

$[-](\text{CH}_2)_n\text{-SA'}$



(corresponding to a number h) n being an integer from 1 to 6

with $[.]i = u + j + k + h$

$[.]$ total number of $\alpha \text{NH}_3^+ = p = u - q$

$[.]$ total number of $\omega \text{NH}_3^+ = j = f - (k + h)$

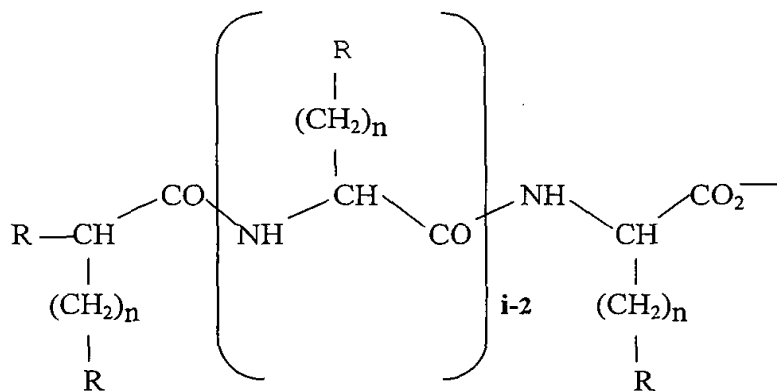
$[.]$ total number of $\text{NH}_3^+ = m = p + j + 1$

with the proviso that :

1) $u \geq i/2$

2) $m \geq i/2$

--7. (amended) [Oligomeric] The oligomeric conjugate according to [anyone of claims] claim 1 [to 6], wherein the oligomeric conjugate contains an oligomer of the following formula:

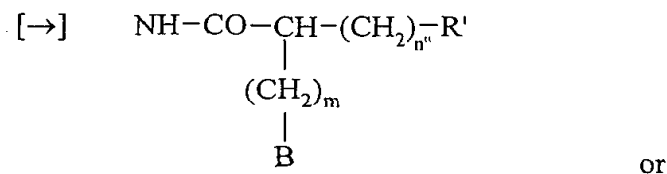
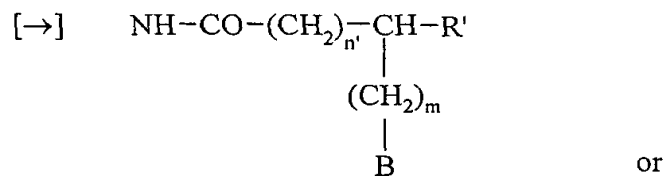


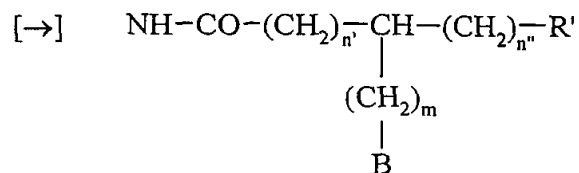
wherein

* i = degree of polymerization from 5 to 36 [50, and particularly 10 to 40, and preferably 20,]

* n = is an integer varying from 1 to 6, [and preferably 4,]

* R represents in a ratio of 50 % to 100 % (corresponding to u)





m is an integer varying from 1 to 6,

n' is an integer varying from 0 to 6,

n'' is an integer varying from 0 to 6,

B is a weak base [as defined according to anyone of claims 2 to 4],

R' represents NH_3^+ (corresponding to a number p),

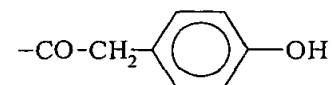
or NH (corresponding to a number q) substituted by
-CO-CH₃

-CO-(CHOH)_rH

r being an integer from 1
to 15, [and preferably
1 to 7]

-CO-(CH₂)_s-(CHOH)_rH

r being an integer from 1
to 15, [and preferably 1 to
7,] and s being an integer
from 1 to 6, [and
preferably 6]



-SO₂-Flu

-CO-Flu

-CS-NH-Flu

Flu being a fluorescent molecule

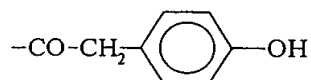
* R represents in a ratio of 0 % to 50 % (corresponding
to f : 0 < f ≤ 1)

$[-]\text{NH}_3^+$ (corresponding to a number j),

$[-]NH$ (corresponding to a number k), substituted by
 $-CO-CH_3$

$-CO-(CHOH)_rH$ r being an integer from 1 to 15, [and preferably 1 to 7]

$-CO-(CH_2)_s-(CHOH)_rH$ r being an integer from 1 to 15, [and preferably 1 to 7,] and s being an integer from 1 to 6[, and preferably 6]



$-SO_2-Flu$

$-CO-Flu$

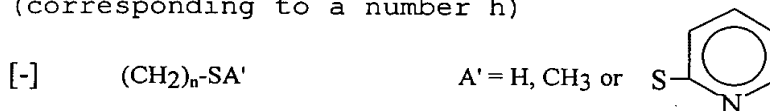
$-CS-NH-Flu$

Flu being a fluorescent molecule

$[-]H$ (corresponding to a number h)

$[-](CH_2)_nH$, n being an integer from 1 to 6
 (corresponding to a number h)

$[-](CH_2)_n-OH$ n being an integer from 1 to 6
 (corresponding to a number h)



(corresponding to a number h) n being integer from 1 to 6

with $[.]i = u + j + k + h$

$[.]total \text{ number of } \alpha NH_3^+ = p = u - q$

$[.]total \text{ number of } \omega NH_3^+ = j = f - (k + h)$

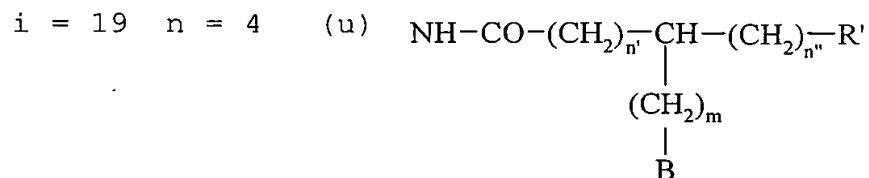
$[.]total \text{ number of } NH_3^+ = m = p + j + 1$

with the proviso that :

1) $u \geq i/2$

2) $m \geq i/2$

--8. (amended) [Oligomeric] The oligomeric conjugate according to [anyone of claims] claim [1 to] 7, [wherein the oligomeric conjugate contains an oligomer of the formula according to claim 7,] wherein



wherein

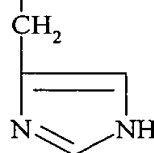
$$n' = n'' = 0$$

$$\text{R}' = \text{NH}_3^+$$

$$m = 1$$

$$\text{B} = \text{imidazole}$$

$$\text{R} = \text{NH-CO-CH-NH}_3^+$$

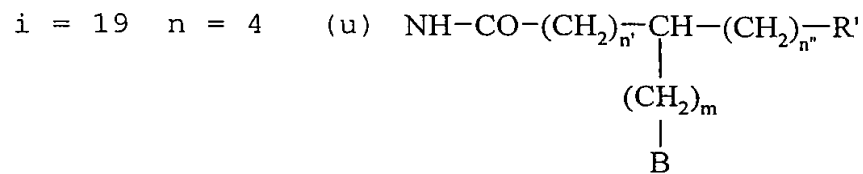


$$(f) \quad \text{R} = \text{NH}_3^+$$

$$u = 12$$

$$j = 7$$

or



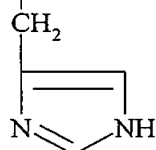
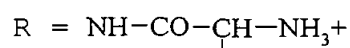
wherein

$$n' = n'' = 0$$

$$R' = \text{NH}_3^+$$

$$m = 1$$

$$B = \text{imidazole}$$

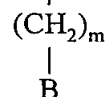
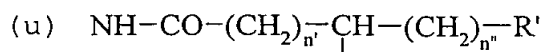


$$(f) R = \text{NH}_3^+$$

$$u = 16$$

$$j = 3$$

$$i = 19 \quad n = 4$$



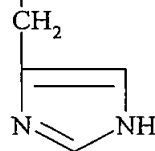
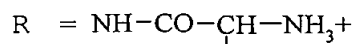
Wherein

$$n' = n'' = 0$$

$$R' = \text{NH}_3^+$$

$$m = 1$$

$$B = \text{imidazole}$$

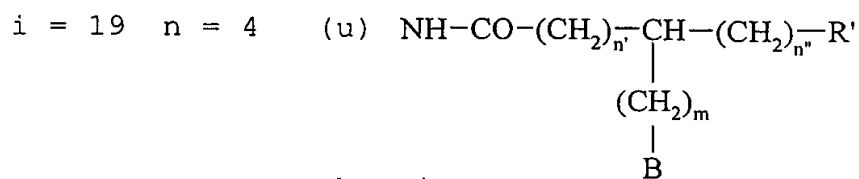


$$(f) R = \text{NH}_3^+$$

$$u = 19$$

$$j = 0$$

or



wherein

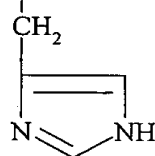
$$n' = n'' = 0$$

$$\text{R}' = \text{NH}_3^+$$

$$m = 1$$

$$\text{B} = \text{imidazole}$$

$$\text{R} = \text{NH-CO-CH-NH}_3^+$$

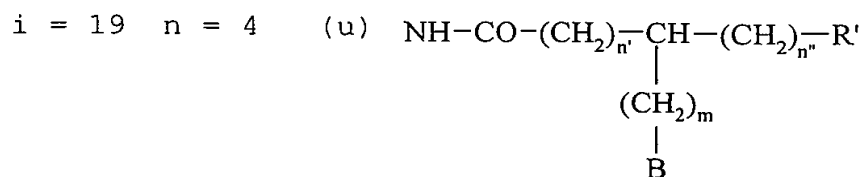


$$(f) \quad \text{R} = \text{CO-CH}_3$$

$$u = 11$$

$$k = 8$$

or



wherein

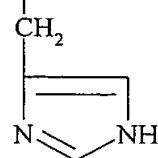
$$n' = n'' = 0$$

$$\text{R}' = \text{NH}_3^+$$

$$m = 1$$

$$\text{B} = \text{imidazole}$$

$$\text{R} = \text{NH-CO-CH-NH}_3^+$$

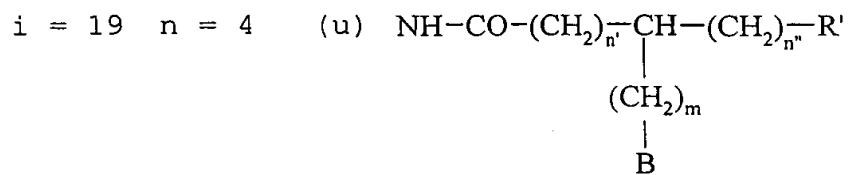


$$(f) \quad \text{R} = \text{CO-CH}_3$$

$$u = 15$$

$$k = 4$$

Or



wherein

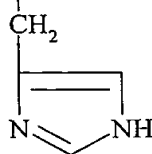
$$n' = n'' = 0$$

$$\text{R}' = \text{NH}_3^+$$

$$m = 1$$

$$\text{B} = \text{imidazole}$$

$$\text{R} = \text{NH-CO-CH-NH}_3^+$$



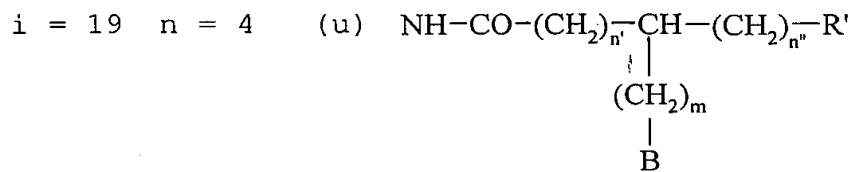
$$(f) \quad \text{R} = \text{CO-(CHOH)}_r\text{H}$$

$$r = 5$$

$$u = 12$$

$$k = 3$$

or



wherein

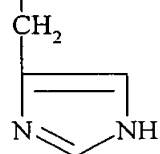
(q) $n' = n'' = [2]0$

$R' = \text{NH-CO-CH}_3$

$m = 1$

$B = \text{imidazole}$

$R = \text{NH-CO-CH-NH}_3^+$



(f) $R = \text{NH}_3^+$

$u = 16$

$f = 4$

$k = 3$

--9. (amended) [Composition] A composition
[containing at least one] comprising an oligomeric conjugate
according to [anyone of claims 1 to] claim 8, in association
with at least one biological molecule, [such as a] selected
from the group consisting of a peptide, an oligoside, [or]
an oligonucleotide, [or] and a mixture thereof.

--10. (amended) [Combined] A combined preparation
[containing as active substance the following individual
components], in the form of a kit-of-parts [:], comprising

- an oligomeric conjugate according to [anyone of
claims] claim 1 [to 8], and

- [at least one oligomeric conjugate according to
anyone of claims 1 to 8, in association with at least one] a
biological molecule, [such as] selected from the group
consisting of a peptide, an oligoside, [or] an
oligonucleotide, [or] and a mixture thereof,

for the simultaneous, separate or sequential use, for

the *in vitro*, [the] *in vivo*, or [the] *ex vivo* transfer of said biological molecules into [the] a cytosol and/or cell nucleus.--

--11. (amended) [Use of an oligomeric conjugate according to anyone of claims 1 to 8,] A method for the *in vitro*, [the] *ex vivo*, or [the] *in vivo* intracellular transfer of biological molecules into [the] a cytosol and/or in [the] a cell nucleus of a cell, comprising:

treating said cell with an oligomeric conjugate according to claim 1 in association with a biological material.--

--12. (amended) [Use of an oligomeric conjugate according to anyone of claims 1 to 8 or of a composition according to claim 9, or of a combined preparation according to claim10,] A method for the [intracellular the] *in vitro*, [the] *ex vivo*, or [the] *in vivo* transfer of a peptide, an oligoside or an oligonucleotide, or a mixture thereof, into [the] a cytosol [or/]and/or [in the] a cell nucleus of a cell, comprising: .

treating said cell with an oligomeric conjugate according to claim 1 in association with said peptide, oligoside, oligonucleotide and mixture thereof.--

--13. (amended) [Use of an oligomeric conjugate according to anyone of claims 1 to 8 or of a composition according to claim 9, or of a combined preparation according to claim10] The method according to claim 11, wherein the cells are [chosen among] selected from the group consisting of muscular, epithelial, endothelial, and myeloid cells [such as monocytes, macrophages and fibroblasts, leukocytes and granulocytes, osteoblasts as well as dendritic cells, stem cells, neuronal cells, or dermal cells].

--14. (amended) [Method] A method for the *in vivo*, [the] *in vitro* or [the] *ex vivo* transfer of an oligonucleotide, [wherein] comprising contacting an oligonucleotide and an oligomeric conjugate according to [anyone of claims] claim 1 [to 8 or of a composition according to claim 9, or of a combined preparation according to claim 10, are(is) contacted] with a medium containing cells [to be transferred], [under conditions such that there is] wherein:

[- transfer of] an antisense oligonucleotide is transferred into [in the] a cytosol and/or the cell nucleus where it binds and blocks the complementary mRNA sequence[.];

[- or transfer of] an oligonucleotide [as activator] is transferred into [the] a cytosol where it depresses or activates a [second] messenger in [the] a cytosol, or the corresponding gene in the nucleus[.];

[- or transfer into the cytosol and/or the cell nucleus of] oligonucleotides corresponding to a repetitive bacterial type DNA sequence with stimulating or immunodepressive activity are transferred into a cytosol and/or cell nucleus of a cell[.];

[- or transfer of] an oligonucleotide [in] is transferred into the cell nucleus where it binds to DNA and forms a triple helix leading to the inhibition of gene expression[.];

[- or transfer into the cytosol and/or the cell nucleus of RNA] oligonucleotides are transferred into a cytosol and/or cell nucleus [acting as decoys] which inhibit gene expression by blocking the binding of regulatory factors to the specific [authentic] DNA region[.]; or

[-or transfer into the cytosol and/or the cell nucleus of] ribozymes (RNA oligonucleotides) which inhibit gene expression by cleaving the mRNA are transferred into a cytosol, and/or cell nucleus.--

--17. (amended) [Pharmaceutical] A pharmaceutical composition, comprising as an active substance, [at least] an oligomeric conjugate according to [anyone of claims] claim 1 [to 8], [or of a composition according to claim 9, or of a combined

preparation according to claim 10, or] in association with a pharmaceutically acceptable vehicle.

--19. (amended) [Kit]. A kit or case [containing] comprising :

[-] a) an oligomeric conjugate according to [anyone of claims] claim 1 [to 8], substituted by [a] protonable residues, said residues being protonated in a weak acid medium, said protonation leading to destabilization of cellular membranes [leading in a weak acid medium to a destabilization of cellular membranes, this] said oligomeric conjugate being able to comprise a recognition signal, which is previously fixed or not on [the above-said] said conjugate, wherein said recognition signal [being dependent upon the cell to target,] is a ligand for a cell membrane receptor

[-] b) at least one biological molecule to transfer,

[-] c) optionally reagents enabling the possible binding of the recognition signal on the above-said oligomeric conjugate,

[- optionally reagents enabling the formation of a composition according to claim 9, or of a combined preparation according to claim 10,]

[-] d) reagents enabling the transfer of the biological molecule in the cytosol and/or the cell nucleus.-